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Advances in Biological Markers for Cancer

J. V. KLAVINS, M.D., PH.D.

Department of Pathology,
The Catholic Medical Center
of Brooklyn and Queens, Inc.
Jamaica, NY 11432

ABSTRACT

The following serum tumor markers are elevated above normal levels in 50 percent or more of patients with various malignant neoplasms: *Alpha-fetoprotein* in yolk sac tumors, hepatomas, retinoblastomas, embryonal carcinomas, breast carcinomas, and carcinomas of uterine cervix; *Carcinoembryonic antigen* in colon carcinomas, choriocarcinomas, pancreatic carcinomas, medullary thyroid carcinomas, osteosarcomas, retinoblastomas, ovarian cystadenocarcinomas, mycosis fungoides, hepatomas, esophageal carcinomas, adenocarcinomas of uterine cervix, lung carcinomas, carcinomas of small intestine, urinary bladder carcinomas, and renal cell carcinomas; *Human chorionic gonadotrophin* in choriocarcinomas, malignant interstitial cell tumors of testis, non seminomatous tumors of testis, embryonal carcinomas, and pancreatic carcinomas.

Combined use of these three markers increases the probability of finding one of them to be elevated in selected cases of malignancy. There will be further advances in biological markers for cancer, but the existance of a specific marker is questionable.

Introduction

In the past, malignant neoplasms were distinguished from normal tissues mainly by the application of the classical morphological criteria as observed with the light microscope. Later, with the addition of various histochemical and electron microscopic procedures, particular kinds of cancers became more easily recognized.

More recently, in parallel with morphologic studies of cancers such as investigations of chromosome abnormalities, the search for biochemical markers has intensified. From these investigations, three groups of markers have emerged: oncofetal, tumor associated, and possibly tumor specific.[29,30]

Many efforts have been directed towards isolation of a tumor specific marker which could be measured and presented in qualitative and quantitative terms. Although many tumor specific markers have been suggested, extended studies have shown them to be nonspecific, either tumor associated or embryonal gene products. There are many such oncofetal and tumor associated markers.

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Clinical Application of Universal Oncofetal Tumor Markers

All tumor markers represent two subgroups: universal, present in malignant neoplasms which are derived from any of the three germinal layers, and those with limited distribution.[29,30]

The best known and widely used universal oncofetal tumor markers are alphafetoprotein (AFP), carcinoembryonic antigen (CEA), and human chorionic gonadotrophin (HCG). They have been clinically used in the investigation of patients with neoplasms of the liver, colon, and trophoblast, respectively. However, the universal nature of their presence in different malignant neoplasms is less well known. This property indicates the use of any of these three markers in the investigation of patients with tumors other than those mentioned previously. Furthermore, testing for all three markers will increase the probability of detecting at least one as being produced by the tumor. The cell population in a given malignant neoplasm is heterogenous and, therefore, the production of markers is variable not only in their quantity but in the kind of the gene product being expressed.

TABLE I

Incidence of Elevated serum Alpha-fetoprotein in Different Malignant Neoplasms

Neoplasms	*Percent*	*Reference Number*
Yolk sac tumors	100	*
Hepatomas†	80	9
Retinoblastomas†	80	39
Embryonal carcinomas‡	73	33
Breast carcinomas§	59	17
Carcinomas of the uterine cervix§	57	17
Carcinomas of pancreas§	23	57
Melanomas‡	20	40
Gastric carcinomas§	15	36
Basal cell carcinomas	13	34
Bronchogenic carcinomas	7	57
Leukemias	6	40
Colon carcinomas	5	57
Nasopharyngeal carcinomas	2	34

*Klavins, J.V., unpublished data, 1982.
†Combined with carcinoembryonic antigen determination - see table IV.
‡Combined with human chorionic gonadotrophin - see table V.
§Combined with carcinoembryonic antigen and human chorionic gonadotrophin - see table VII.

As indicated in table I, serum AFP is elevated above normal values in all patients with yolk sac tumors and in 80 percent of patients with hepatomas and retinoblastomas. This marker can be detected in sera of patients with other cancers as well.

The incidence of elevated serum CEA

TABLE II

Incidence of Elevated Serum Carcinoembryonic Antigen in Different Malignant Neoplasms

Neoplasms	*Percent*	*Reference Number*
Colon carcinomas	100	18
Choriocarcinomas*	100	37
Pancreatic carcinomas†	85	43
Medullary thyroid carcinomas	85	21
Familial medullary thyroid carcinomas	84	11
Osteosarcomas	81	15
Retinoblastomas‡	80	39
Ovarian cystadenocarcinomas§	77	26
Mycosis fungoides	75	1
Hepatomas‡	70	20
Esophageal carcinomas	70	2
Adenocarcinomas of the uterine cervix	68	28
Lung carcinomas†	67	6
Carcinomas of small intestine	67	24
Urinary bladder carcinomas§	60	60
Renal cell carcinomas	56	14
Neural crest tumors	43	19
Breast carcinomas†	42	23
Prostatic carcinomas¶	40	13
Primary uveal melanomas	36	38
Neuroblastomas	35	22
Fluids with malignancy§	34	48
Seminomas§	33	50
Basal cell carcinomas	33	1
Gastric carcinomas†	32	27
Laryngeal carcinomas	31	3
Endometrial carcinomas§	30	54
Uterine cervix intraepithelial carcinomas†	29	55
Carcinomas of buccal mucosa	27	3
Craniopharyngiomas	25	4
Embryonal rhabdomyosarcomas	24	22
Carcinomas of oropharynx	23	3
Brain tumors	22	41
Testicular teratomas	9	56

*Human chorionic gonadotrophin is more specific for this tumor
†Combined with alpha-fetoprotein and human chorionic gonadotrophin - see table VII.
‡Combined with alpha-fetoprotein - see table IV.
§Combined with human chorionic gonadotrophin - see table VI.
¶Prostatic acid phosphatase is more specific for this tumor.

TABLE II

rated Serum Carcinoembryonic
ferent Malignant Neoplasms

	Percent	Reference Number
	100	18
	100	37
† cinomas	85	43
	85	21
yroid		
	84	11
	81	15
	80	39
inomas§	77	26
	75	1
	70	20
	70	2
a uterine		
	68	28
	67	6
ntestine	67	24
nomas§	60	60
	56	14
	43	19
	42	23
	40	13
as	36	36
	35	22
y§	34	46
	33	50
	33	1
	32	27
	31	3
s§	30	54
pithelial		
	29	55
mucosa	27	3
	25	4
rcomas	24	22
ynx	23	3
	22	41
	9	56

dotrophin is more specific for

fetoprotein and human chorionic
table VII.
fetoprotein - see table IV.
chorionic gonadotrophin - see

hatase is more specific

roduction of markers is
in their quantity but in
gene product being ex-

n table I, serum AFP is
normal values in all pa-
sac tumors and in 80
nts with hepatomas and
This marker can be de-
patients with other can-

of elevated serum CEA

in different malignant neoplasms is listed in table II. Although used alone, it is a useful marker for colon carcinomas; it can also be used by itself and in combination with additional tumor markers for the investigation of other neoplasms. For example, in pancreatic carcinoma, a tumor difficult to diagnose, serum CEA is elevated in 85 percent, HCG in 50 percent and AFP in 23 percent of the patients. Thus, measurement of all three markers increases the probability that abnormal amounts of one of them might be detected.

Human chorionic gonadotrophin, as can be seen from table III, is also a marker for tumors other than those of germ cell origin.

The probability of detecting in patients' serum a marker for a given neoplasm increases with the use of a combination.[31,35] Various combinations to detect a marker for certain tumors are indicated in tables IV, V, VI, and VII.

A universal oncofetal tumor marker widely used in Europe, but not yet in the United States, is tissue polypeptide antigen.[8] It is associated with cell proliferation and is not specific for any species.

TABLE III

Incidence of Elevated Serum Human Chorionic Gonadotrophin in Different Malignant Neoplasms

Neoplasms	Percent	Reference Number
Choriocarcinomas	100	*
Malignant interstitial cell tumors of testis	100	52
Non seminomatous tumors of testis†	68	25
Embryonal carcinomas†	56	10
Pancreatic carcinomas‡	50	10
Teratomas	44	*
Ovarian adenocarcinomas§	40	53
Uterine cervix carcinomas‡	31	45
Endometrial carcinomas§	24	45
Seminomas§	24	7
Gastric carcinomas‡	24	10
Urinary bladder carcinomas§	22	12
Breast carcinomas‡	21	53
Colorectal carcinomas¶	16	12
Bronchogenic squamous cell carcinomas‡	14	12
Melanomas†	10	10
Multiple myelomas	6	10

*Klavins, J.V., unpublished data, 1982.
†Combined with alpha-fetoprotein - see table V, "Non seminomatous germ cell tumors"
‡Combined with alpha-fetoprotein and carcinoembryonic antigen - see table VII.
§Combined with carcinoembryonic antigen - see table VI.
¶Carcinoembryonic antigen is more specific for this tumor.

TABLE IV

Suggested Combined Use of Alpha-fetoprotein and Carcinoembryonic Antigen

	Incidence in Percent	
Neoplasm	AFP	CEA
Retinoblastomas	80	80
Hepatomas	80	70

Future Prospects

The ideal marker would be one that is specific and universal. Such a marker may not exist if malignant transformation is not associated with the expression of a unique gene product by all kinds of transformed cells. A potential specific marker for certain T cell leukemias and lymphomas has been recently described.[49] It is a human oncogenic ribonucleic acid virus. Thus, the existence of a specific marker with a limited distribution is established. This marker deviates from the general definition of tumor markers[29] because it is not a product

TABLE V

Suggested Combined Use of Alpha-fetoprotein and Human Chorionic Gonadotrophin

	Incidence in Percent			
Neoplasm	AFP	HCG	Either AFP or HCG	Reference
Non seminomatous germ cell tumors	60	68	94	25
Primary intracranial germ cell tumors	36	29	50	5
Melanomas	20	10		

TABLE VI

Suggested Combined Use of Carcinoembryonic Antigen and Human Chorionic Gonadotrophin

	Incidence in Percent			
Neoplasm	CEA	HCG	Either CEA or HCG	Reference
Fluids with malignancy	47	36	69	16
Ovarian carcinomas	77	40		
Urinary bladder carcinomas	60	22		
Seminomas	33	24		
Endometrial carcinomas	30	24		

of a tumor but is a non-endogenous type C retrovirus.[47]

It is probable that there is no expression of a unique cellular gene product but that there is an augmented production of certain oncogene or onc protein which characterizes the malignant phenotype.[38] This exaggerated expression would certainly appear to be determined by some alteration in the genetic structure of the transformed cells. The oncogene might be a gene regulating, in some way, the embryonic differentiation of its product which, subsequently expressed in excess, would produce the cancer phenotype.

The possibility of a unique site of genetic alteration is suggested by the experiments of Shilo and Weinberg[51] who found the transforming gene was common for four, independently produced 3-methylcholanthrene transformed mouse fibroblast lines, and the carcinogen led to the activition of a specified gene. In such an experimental model, mouse fibroblasts are maintained in culture for an indefinite growth. Thus, they may already be preconditioned for the transformation event to take place.

Recently, Perucho and associates[46] have shown that there are closely related or identical transforming genes in deoxyribonucleic acid (DNA) of one human colon and two lung carcinomas. On the other hand, a cell line from a bladder carcinoma in the experiments contained a different transforming gene from another cell line studied earlier.[32] There is also evidence of the presence of separate different oncogenes for other human malignant neoplasms.[42]

Some new tumor markers may be detected by transfection studies using tumor DNA. One such tumor-associated protein, induced by a transforming DNA of rat neuroblastomas and glioblastomas, is a 185,000 dalton phosphoprotein.[44] More recently,[39] evidence has been obtained of a unique oncogene with a correspondingly abnormal protein in bladder carcinoma. This might be a specific tumor marker, if future studies do not detect a similar entity in normal embryonal cells.

TABLE VII

Suggested Combined Use of Alpha-fetoprotein, Carcinoembryonic Antigen and Human Chorionic Gonadotrophin

	Incidence in Percent		
Neoplasm	AFP	CEA	HCG
Pancreatic carcinomas	23	85	50
Carcinomas of the uterine cervix	57	68	31
Breast carcinomas	59	42	21
Bronchogenic carcinomas	7	67	14
Gastric carcinomas	15	32	24

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Oncogenes as Markers for Early Detection of Cancer

Geoffrey M. Cooper

Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115

Abstract Oncogenes are formed in human tumors as a result of mutations or DNA rearrangements leading to the abnormal expression or function of proto-oncogenes. Approximately 20 different oncogenes are reproducibly activated in malignancies of several types, including breast, colon, lung, pancreatic, and thyroid carcinomas, leukemias, and lymphomas. The potential utility of these oncogenes as markers for early detection of cancer is dependent on the stage of tumor development at which they are activated, and on whether the mutated oncogenes are readily distinguished from the corresponding proto-oncogenes by assays that are sufficiently sensitive to detect precancerous lesions.

Key words: *abl*, chemoprevention, colorectal carcinoma, intermediate biomarker, leukemia, oncogenes, polymerase chain reaction, *ras*, tumor suppressor genes

It is now widely recognized that human tumors result from accumulated genetic damage leading to the activation of oncogenes and the loss or inactivation of tumor suppressor genes. Since mutations in these genes represent critical events in tumorigenesis, it is reasonable to expect that such mutations might also prove useful as markers of tumor development. This article will provide a brief review of oncogenes and discuss their potential application as early markers of neoplasia. In considering the applicability of oncogenes as markers of tumor development, at least three points need to be addressed: 1) How frequently are specific oncogenes activated in different types of tumors?, 2) At what stage of tumor development does oncogene activation occur?, and 3) How readily can oncogene activation be detected?

MECHANISMS OF CELLULAR ONCOGENE ACTIVATION

Oncogenes were first identified as specific genes of acutely transforming retroviruses that induced transformation of virus-infected cells. Subsequently, cellular oncogenes were identified by three approaches: (1) as homologs of retroviral oncogenes, (2) as genes that induce transformation upon introduction into appropriate recipient cells by transfection, and (3) as genes that are frequently altered in tumors by DNA rearrangement or amplification. Together, these approaches have identified more than 70 cellular genes that, as activated oncogenes, can induce at least some aspects of the tumorigenic phenotype [1].

Oncogenes are formed from normal cellular genes (proto-oncogenes) as a consequence of genetic alterations that result in either abnormal gene expression or the synthesis of altered proteins. In some cases, altered expression of a normal gene product is sufficient to convert a proto-oncogene to a biologically active oncogene. In other cases, the oncogene proteins differ in structure and function from those encoded by proto-oncogenes. The mechanisms by which oncogenes are activated in tumors is an important consideration in terms of their potential detection as early markers of tumor development.

One mechanism that can result in elevated expression of an oncogene is gene amplification, which results in an increased number of gene copies per cell. Elevated gene expression is then a direct result of an increased number of templates available for transcription. In this case, there are no distinct structural differences between the oncogene and the proto-oncogene. Consequently, detection of an amplified oncogene is possible only by quantitation of copy number in tumor cells.

Alternatively, abnormal gene expression can result from DNA rearrangements, such as chromosome translocations. The prototype

example of oncogene activation by this mechanism is translocation of the c-myc gene in Burkitt's lymphomas from its normal locus on chromosome 8 to one of the immunoglobulin gene loci on chromosomes 2, 14, and 22 [2]. This results in a loss of normal gene regulation, leading to constitutive expression of the normal c-myc protein. The translocations resulting in activation of c-myc, and other oncogenes that are deregulated in a similar manner, can occur over a broad region of DNA. Thus, like gene amplification, these translocations do not result in the formation of a distinct molecular marker of oncogene activation.

Other translocations, however, result in the formation of oncogenes that have suffered reproducible structural alterations, leading to formation of an altered gene product. These oncogenes encode recombinant fusion proteins, formed by recombination between coding sequences of two distinct genes. The activation of the abl oncogene by the Philadelphia translocation in chronic myelogenous leukemia is an example of such a DNA rearrangement [3]. In this translocation, the abl proto-oncogene from chromosome 9 recombines with another gene, bcr, on chromosome 22. As a result of this rearrangement, the amino-terminal sequences of abl are deleted and replaced with bcr coding sequences. The recombinant bcr/abl oncogene protein functions in an uncontrolled manner, leading to the development of neoplasia. Since the recombination event occurs in a defined region of both the abl and bcr genes, the recombinant transcript represents a unique fusion between abl and bcr sequences. Consequently, the oncogene bcr/abl mRNA can be sensitively detected using polymerase chain reaction (PCR) primers that span the recombination site [4]. Similar DNA rearrangements lead to the activation of several other oncogenes in human tumors, including the retinoic acid receptor in acute promyelocytic leukemias [5,6].

Other oncogenes are activated by point mutations rather than DNA rearrangements. The ras oncogenes, for example, are activated by point mutations leading to single amino acid substitutions at critical positions in the ras gene products [7]. Such single amino acid substitutions result in deregulation of ras protein function, converting a normally regulated proto-oncogene protein into an oncogene protein that is constitutively active. Similar point mutations are responsible for activation of the gsp and gip oncogenes in some hormone-responsive human tumors [8]. Such point mutations can also be sensitively detected by PCR analysis, using mutation-specific PCR primers or oligonucleotide probes [9].

ONCOGENE FUNCTIONS

Most proto-oncogenes are normally expressed in a wide variety of cell types, where they function to regulate normal cell proliferation in response to mitogenic stimuli. The proteins encoded by almost all of the characterized oncogenes can be divided into five functional groups, which act as regulatory elements in signal transduction pathways leading to cell proliferation (Table 1) [10]. Whereas the proto-oncogene products function in normal cell proliferation, the unregulated expression or activity of the oncogene proteins leads to a loss of normal growth control and tumor development.

First, a number of oncogenes encode extracellular growth factors. The prototype of this group of oncogenes is sis, the oncogene of simian sarcoma virus, which encodes the B chain of platelet-derived growth factor. Other members of this group of oncogenes include several members of the fibroblast growth factor family and hematopoietic growth factors. Transformation by these oncogenes is a consequence of abnormal growth factor expression by a responsive cell, leading to autocrine stimulation of cell growth.

The second major group of oncogenes encode protein-tyrosine kinases. There are two classes of these proteins. The receptor protein kinases are membrane-spanning molecules that function as growth factor receptors. The erbB oncogene, which is derived from the EGF receptor, is the prototype of this group. A closely related gene, erbB-2, is frequently amplified in human breast and ovarian carcinomas [11]. Other receptor protein-tyrosine kinases include ret and trk, which are frequently activated in human thyroid carcinomas [12,13]. The nonreceptor protein-tyrosine kinases, including abl, are intracellular molecules. Many of these proteins are associated with the inner face of the plasma membrane where they may function in noncovalent association with cell surface receptors.

The third group of oncogene proteins, guanine nucleotide binding proteins,

TABLE I. Oncogene Functional Groups

Functional Activity	Representative Oncogenes
Growth Factors	sis, FGF, int-1, int-2, hst, fgf-5, IL-2, IL-3, CSF-1, GM-CSF
Protein-Tyrosine Kinases	
Receptor	erbB, erbB-2, fms, ros, trk, met, kit, ret, sea
Nonreceptor	src, yes, fgr, lck, fyn, lyn, hck, abl, fes
GTP Binding	rasH, rasK, rasN, gip, gsp
Protein-Serine/Threonine Kinases	mos, pim-1, c-raf, A-raf, B-raf
Transcription Factors	erbA, c-jun, jun-B, jun-D, c-fos, fra-1, fos-B, c-myc, L-myc N-myc, myb, ets, E2A, RAR, rel

includes the ras gene products, which are the oncogenes most frequently activated in human tumors [14]. The ras proteins are localized to the inner face of the plasma membrane and are thought to function in signal transduction from growth factor receptors to second messengers, which still remain unidentified in mammalian cells. The activity of the ras proteins is controlled by GTP/GDP binding and hydrolysis, analogous to the G proteins that serve to regulate adenylate cyclase and other enzymes affecting the metabolism of intracellular second messengers [15,16]. The genes encoding Gs and Gi, gsp and gip, also act as oncogenes in some hormone-responsive cells, such as ovarian and pituitary tumors.

Other oncogenes encode protein-serine/threonine kinases that are cytosolic enzymes. These oncogenes include members of the raf family, which are activated in response to growth factor stimulation of a variety of cell types [17].

Finally, a large number of oncogenes encode nuclear proteins, many of which have been shown to function as transcriptional regulatory factors [18]. These include the fos and jun oncogene products, which comprise the AP-1 transcription factor, as well as members of the myc gene family, which are frequently activated by DNA rearrangement or gene amplification in a variety of human neoplasms. The erbA oncogene, which encodes thyroid hormone receptor, and the RAR oncogene, which encodes retinoic acid receptor, are also members of this group.

Most oncogene products can thus be viewed as regulatory elements in intracellular signal transduction pathways leading to cell proliferation. Extracellular growth factors act to stimulate the enzymatic activity of receptor protein-tyrosine kinases, which then transmit a mitogenic signal via activation of ras gene products, the raf protein-serine/threonine kinase, and phospholipase C, resulting in formation of diacylglycerol and activation of protein kinase C. The activity of these cytosolic protein-serine/threonine kinases ultimately affects the activity and expression of transcriptional regulatory proteins in the nucleus, leading to changes in gene expression and cell division.

ONCOGENES IN HUMAN TUMORS

Although more than 70 oncogenes have been identified, not all of these are frequently encountered in human neoplasms. Reproducible activation of about 20 oncogenes has so far been described in human tumors, and these genes, which represent potential markers of human neoplasia, are indicated in Table 2.

Some of these oncogenes are activated highly reproducibly in specific types of tumors, and their activation appears to play a role in the genesis of nearly all individual neoplasms of these types. Such oncogenes include abl in chronic myelogenous leukemia, bcl-2 in follicular B-cell lymphomas, c-myc in Burkitt's lymphomas, and the retinoic acid receptor (RAR) in acute promyelocytic leukemia. Other oncogenes are activated in only a fraction of individual neoplasms of the types of tumors in which they are involved, including the ras genes in colon and lung carcinomas. In some

TABLE II. Oncogenes Activated in Human Tumors

Oncogene	Neoplasm	Activation Mechanism
abl	chronic myelogenous leukemia acute lymphocytic leukemia	translocation
bcl-2	follicular B-cell lymphoma	translocation
bcl-3	chronic B-cell leukemia	translocation
can	acute nonlymphocytic leukemia	translocation
E2A	acute lymphocytic leukemia	translocation
erbB-2	breast and ovarian carcinoma	amplification
gip	adrenal cortical and ovarian carcinoma	point mutation
gli	glioblastoma	amplification
gsp	pituitary carcinomas	point mutation
hox-11	acute lymphocytic leukemia	translocation
lyl	acute lymphocytic leukemia	translocation
c-myc	Burkitt's lymphoma breast and lung carcinoma	translocation amplification
N-myc	neuroblastoma, lung carcinoma	amplification
L-myc	lung carcinoma	amplification
RAR	acute promyelocytic leukemia	translocation
rasH	thyroid carcinoma	point mutation
rasK	colon, lung, pancreatic, and thyroid carcinomas	point mutation
rasN	acute myeloid and lymphoid leukemia thyroid carcinomas	point mutation
ret	thyroid carcinoma	rearrangement
rhom	acute lymphocytic leukemia	translocation
scl	acute stem cell leukemia	translocation
tan	acute lymphocytic leukemia	translocation
trk	thyroid carcinoma	rearrangement

cases, activation of these oncogenes is correlated with differences in tumor behavior. For example, amplification of N-myc in neuroblastomas is found in more aggressive tumors and is correlated with progression to increasing malignancy [19]. Amplification of erbB-2 is similarly correlated with the malignancy of breast and ovarian carcinomas [11].

Different oncogenes are often involved in different stages of tumor development. Carcinogenesis is clearly a multistep process, which frequently occurs as a consequence of accumulated damage to both oncogenes and tumor suppressor genes. Some oncogenes are involved in early stages of tumorigenesis, whereas others appear to be involved in later stages of tumor progression. In several types of neoplasms, ras oncogenes appear to play a role in early stages of tumorigenesis. For example, ras oncogenes are activated by mutations characteristic of those induced by the initiating carcinogen in a variety of experimental animal tumors, suggesting that ras genes are targets for carcinogen-induced mutations at the initiation stage of tumor development [7]. Likewise, ras oncogenes are activated at early stages of the development of several human neoplasms. In colorectal carcinomas, for example, activation of rasK and inactivation of the APC and MCC tumor suppressor genes appear to be early events leading to the development of premalignant adenomas, whereas inactivation of the DCC and p53 tumor suppressor genes usually occurs at later stages of progression to malignancy [20]. Activation of ras oncogenes similarly appears to occur as an early event, preceding malignancy, in thyroid carcinomas and some leukemias [7,14]. In addition, ras oncogenes are characterized by different mutations in different types of cancers (e.g., colon and lung carcinomas), suggesting that ras genes may be targets for carcinogen-induced mutations in these human tumors as well as in experimental animal neoplasms [14]. Detection of ras oncogene mutations may therefore provide a marker for early stages of development of a significant fraction of human cancers.

In contrast, other oncogenes appear to be involved in later stages of tumor progression. These oncogenes include N-myc in neuroblastomas; c-myc, N-myc, and L-myc in lung carcinomas; and erbB-2 in breast and ovarian carcinomas. Since these oncogenes are activated relatively late in tumor progression, they do not constitute markers suitable for early detection.

EARLY DETECTION OF HUMAN TUMORS

In solid tumors, the ras genes provide the most likely early detection markers, being frequently activated in colon, lung, pancreatic, and thyroid carcinomas. In addition to their activation at early stages of tumor development, the mutations responsible for ras oncogene formation can be readily detected in small amounts of material using PCR amplification [9]. For example, it has been possible to detect ras mutations in mammary glands two weeks after exposure to the chemical carcinogen nitrosomethylurea, well before the onset of neoplasia [21]. The sensitivity of current methods for detection of mutations in ras has been estimated to be sufficient to detect one mutant gene in the presence of 10^5 normal alleles [9]. Thus, analysis of mutant ras genes provides a sensitive assay for early events in carcinogenesis. The erbB-2 oncogene, in contrast, is amplified at late stages of tumor progression, as discussed above. Moreover, since its activity as an oncogene results from gene amplification rather than from distinct mutations, sensitivity of detection would pose a problem.

The ras oncogenes might also be used for early detection of some acute leukemias. In these hematopoietic neoplasms, however, a number of other oncogenes have also been identified [22]. In several cases, these genes are activated by chromosome translocations that result in formation of recombinant fusion proteins. Examples include the activation of abl in chronic myelogenous leukemia and RAR in acute promyelocytic leukemia [3,5,6]. These oncogenes can be detected with high sensitivity by PCR analysis of cDNAs using primers that span the recombination sites joining sequences that were unlinked in normal cells—for example, the recombination site between bcr and abl sequences in the bcr/abl recombinant transcript. Detection of this rearrangement is already being used to monitor recurrence of leukemia following treatment of chronic myelogenous leukemia patients [4], and could provide an assay suitable for early detection as well. Thus, in the leukemias and lymphomas, a number of oncogenes activated as recombinant fusion proteins are candidate markers for early disease detection.

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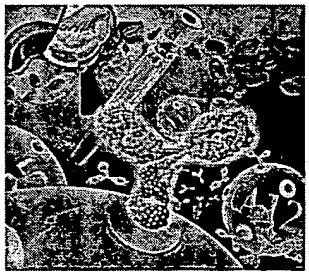
Serum Tumor Markers

GREG L. PERKINS, M.D., EVAN D. SLATER, M.D., GEORGANNE K. SANDERS, M.D., and JOHN G. PRICHARD, M.D., Ventura County Medical Center, Ventura, California

Monoclonal antibodies are used to detect serum antigens associated with specific malignancies. These tumor markers are most useful for monitoring response to therapy and detecting early relapse. With the exception of prostate-specific antigen (PSA), tumor markers do not have sufficient sensitivity or specificity for use in screening. Cancer antigen (CA) 27.29 most frequently is used to follow response to therapy in patients with metastatic breast cancer. Carcinoembryonic antigen is used to detect relapse of colorectal cancer, and CA 19-9 may be helpful in establishing the nature of pancreatic masses. CA 125 is useful for evaluating pelvic masses in postmenopausal women, monitoring response to therapy in women with ovarian cancer, and detecting recurrence of this malignancy. Alpha-fetoprotein (AFP), a marker for hepatocellular carcinoma, sometimes is used to screen highly selected populations and to assess hepatic masses in patients at particular risk for developing hepatic malignancy. Testing for the beta subunit of human chorionic gonadotropin (β-hCG) is an integral part of the diagnosis and management of gestational trophoblastic disease. Combined AFP and β-hCG testing is an essential adjunct in the evaluation and treatment of nonseminomatous germ cell tumors, and in monitoring the response to therapy. AFP and β-hCG also may be useful in evaluating potential origins of poorly differentiated metastatic cancer. PSA is used to screen for prostate cancer, detect recurrence of the malignancy, and evaluate specific syndromes of adenocarcinoma of unknown primary. (Am Fam Physician 2003;68:1075-82. Copyright© 2003 American Academy of Family Physicians.)



See page 1039 for definitions of strength-of-evidence levels.

Because family physicians are assuming a greater role in caring for patients with cancer, an understanding of tumor markers is becoming increasingly important. These soluble molecules in the blood are usually glycoproteins detected by monoclonal antibodies. Each tumor marker has a variable profile of usefulness for screening, determining diagnosis and prognosis, assessing response to therapy, and monitoring for cancer recurrence.

This article describes the use of common tumor markers in primary care practice. Particular emphasis is given to when these tests should be ordered and to common factors that influence the interpretation of tumor marker levels.

Role of Tumor Markers

Screening tests require high sensitivity to detect early-stage disease. These tests also must have sufficient specificity to protect patients with false-positive results from unwarranted diagnostic evaluations.

To date, no tumor marker has demonstrated a survival benefit in randomized controlled trials of screening in the general population. Nevertheless, tumor markers can play a crucial role in detecting disease and assessing response to therapy in selected groups of patients. In monitoring patients for disease recurrence, tumor marker levels should be determined only when there is a potential for meaningful treatment.

Normalization of tumor marker values may indicate cure despite radiographic evidence of persistent disease. In this circumstance, the residual tumor is frequently nonviable. Conversely, tumor marker levels may rise after effective treatment (possibly related to cell lysis), but the increase may not portend treatment failure. However, a consistent increase in tumor marker levels, coupled with lack of clinical improvement, may indicate treatment failure. Residual elevation after

TABLE 1
Conditions Associated with Elevated Tumor Marker Levels

Tumor marker	*Normal value*	*Primary tumor(s)*	*Additional associated malignancies*	*Benign conditions*
CA 27.29[1,2]	< 38 units per mL	Breast cancer	Colon, gastric, hepatic, lung, pancreatic, ovarian, and prostate cancers	Breast, liver, and kidney disorders, ovarian cysts
CEA[3,4]	< 2.5 ng per mL in nonsmokers < 5 ng per mL in smokers	Colorectal cancer	Breast, lung, gastric, pancreatic, bladder, medullary thyroid, head and neck, cervical, and hepatic cancers; lymphoma; melanoma	Cigarette smoking, peptic ulcer disease, inflammatory bowel disease, pancreatitis, hypothyroidism, cirrhosis, biliary obstruction
CA 19-9[5]	< 37 units per mL	Pancreatic cancer, biliary tract cancers	Colon, esophageal, and hepatic cancers	Pancreatitis, biliary disease, cirrhosis
AFP[6]	< 5.4 ng per mL	Hepatocellular carcinoma, nonseminomatous germ cell tumors	Gastric, biliary, and pancreatic cancers	Cirrhosis, viral hepatitis, pregnancy
β-hCG[7,8]	< 5 mIU per mL	Nonseminomatous germ cell tumors, gestational trophoblastic disease	Rarely, gastrointestinal cancers	Hypogonadal states, marijuana use
CA 125[9-11]	< 35 units per mL	Ovarian cancer	Endometrial, fallopian tube, breast, lung, esophageal, gastric, hepatic, and pancreatic cancers	Menstruation, pregnancy, fibroids, ovarian cysts, pelvic inflammation, cirrhosis, ascites, pleural and pericardial effusions, endometriosis
PSA[12-14]	< 4 ng per mL for screening Undetectable level after radical prostatectomy	Prostate cancer	None	Prostatitis, benign prostatic hypertrophy, prostatic trauma, after ejaculation

CA = cancer antigen; CEA = carcinoembryonic antigen; AFP = alpha-fetoprotein; β-hCG = beta subunit of human chorionic gonadotropin; PSA = prostate-specific antigen.

**—The greatest possible sensitivity is 95 percent, given that 5% of the population have Lewis-null blood type and are unable to produce the antigen.*

Information from references 1 through 14.

definitive treatment usually indicates persistent disease. Following tumor marker response is particularly useful when other evidence of disease is not readily accessible.

Cancer Antigen 27.29

Cancer antigen (CA) 27.29 is a monoclonal antibody to a glycoprotein (MUC1) that is present on the apical surface of normal epithelial cells. CA 27.29 is highly associated with breast cancer, although levels are elevated in several other malignancies *(Table 1)*.[1-14] CA 27.29 also can be found in patients with benign disorders of the breast, liver, and kidney, and in patients with ovarian cysts. However, CA 27.29 levels higher than 100 units per mL are rare in benign conditions.[1]

Because of superior sensitivity and specificity, CA 27.29 has supplanted CA 15-3 as the preferred tumor marker in breast cancer. The CA 27.29 level is elevated in approximately one third of women with early-stage breast cancer (stage I or II) and in two thirds of women with late-stage disease (stage III or IV).[2] CA 27.29 lacks predictive value in the earliest stages of breast cancer and thus has no role in screening for or diagnosing the malignancy.

Disagreement exists about the ability of CA 27.29 to detect asymptomatic recurrence after curative treatment. One trial[1] in patients at high risk for recurrence of breast cancer (stage II or III) found that CA 27.29 was highly specific and sensitive in detecting preclinical metastasis. The average time from initial elevation of CA 27.29 to onset of symptoms was five months. Because CA 27.29 testing may lead to prompt imaging of probable sites of metastasis, it may be possible to decrease morbidity through earlier institution of therapy.

Carcinoembryonic Antigen

Carcinoembryonic antigen (CEA), an oncofetal glycoprotein, is expressed in normal mucosal cells and overexpressed

Level above which benign disease is unlikely	*Sensitivity*
> 100 units per mL	Elevated in about 33% of early-stage breast cancers and about 67% of late-stage breast cancers
> 10 ng per mL	Elevated in less than 25% of early-stage colon cancers and 75% of late-stage colon cancers
> 1,000 units per mL	Elevated in 80% to 90% of pancreatic cancers and 60% to 70% of biliary tract cancers*
> 500 ng per mL	Elevated in 80% of hepatocellular carcinomas; Nonseminomatous germ cell tumors: see β-hCG below
> 30 mIU per mL[7]	AFP or β-hCG elevated in 85% of nonseminomatous germ cell tumors; elevated in only 20% of early-stage nonseminomatous germ cell tumors
> 200 units per mL[11]	Elevated in about 85% of ovarian cancers; elevated in only 50% of early-stage ovarian cancers
> 10 ng per mL[12]	Elevated in more than 75 percent of organ-confined prostate cancers[14]

in adenocarcinoma, especially colorectal cancer *(Table 1)*.[1-14] CEA elevations also occur with other malignancies. Nonneoplastic conditions associated with elevated CEA levels include cigarette smoking, peptic ulcer disease, inflammatory bowel disease, pancreatitis, hypothyroidism, biliary obstruction, and cirrhosis. Levels exceeding 10 ng per mL are rarely due to benign disease.[3]

Fewer than 25 percent of patients with disease confined to the colon have an elevated CEA level. Sensitivity increases with advancing tumor stage: CEA values are elevated in approximately 50 percent of patients with tumor extension to lymph nodes and 75 percent of patients with distant metastasis.[4] The highest values (above 100 ng per mL) occur with metastasis,[15] although poorly differentiated tumors are less likely to produce CEA.[4]

CEA is not useful in screening for colorectal cancer or in the diagnostic evaluation of an undefined illness. A CEA level should be ordered only after malignancy has been confirmed. CEA levels typically return to normal within four to six weeks after successful surgical resection.[3]

The major role for CEA levels is in following patients for relapse after intended curative treatment of colorectal cancer. When patients with a normal preoperative CEA level have cancer recurrence, CEA elevation is a sign in nearly one half of them.[4]

The American Society of Clinical Oncology recommends monitoring CEA levels every two to three months for at least two years in patients with stage II or III disease who are surgical candidates.[16] [Evidence level C, consensus/expert guidelines] When an abnormal level is found, the test should be repeated; if CEA elevation is confirmed, patients should undergo imaging of potential recurrence sites. Local recurrence or limited metastasis to liver or lung can be resected with curative intent. Clinical trials examined in one meta-analysis[17] demonstrated a 9 percent (absolute value) improvement in survival after five years in patients who underwent CEA monitoring as part of posttreatment management.

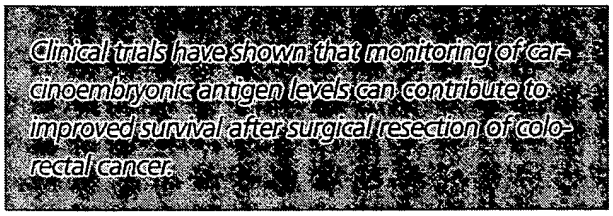
Cancer Antigen 19-9

Elevated levels of CA 19-9, an intracellular adhesion molecule, occur primarily in patients with pancreatic and biliary tract cancers but also have been reported in patients with other malignancies *(Table 1)*.[1-14] This tumor marker has a sensitivity and specificity of 80 to 90 percent for pancreatic cancer and a sensitivity of 60 to 70 percent for biliary tract cancer. Benign conditions such as cirrhosis, cholestasis, cholangitis, and pancreatitis also result in CA 19-9 elevations, although values are usually less than 1,000 units per mL.[5]

Patients with Lewis-null blood type do not produce CA 19-9. Thus, about 5 percent of persons are unable to produce this antigen.[5]

Use of CA 19-9 is limited. The antigen has no value in screening because its positive predictive value is less than 1 percent.[18] However, the positive predictive value of levels over 1,000 units per mL is 97 percent when CA 19-9 test-

One trial found that monitoring of cancer antigen 27.29 levels in patients at high risk for recurrence of breast cancer (stage II or III) was associated with identification of relapse an average of five months before onset of symptoms.



ing is used in clinical situations that are consistent with pancreatic cancer (e.g., jaundice associated with a pancreatic mass). Furthermore, CA 19-9 levels above 1,000 units per mL predict the presence of metastatic disease.[5]

Alpha-Fetoprotein

Alpha-fetoprotein (AFP) is the major protein of fetal serum but falls to an undetectable level after birth. The primary malignancies associated with AFP elevations are hepatocellular carcinoma and nonseminomatous germ cell tumors. Other gastrointestinal cancers occasionally cause elevations of AFP, but rarely to greater than 1,000 ng per mL.[6]

Patients with cirrhosis or viral hepatitis may have abnormal AFP values, although usually less than 500 ng per mL. Pregnancy also is associated with elevated AFP levels, particularly if the pregnancy is complicated by a spinal cord defect or other abnormality.[6]

AFP levels are abnormal in 80 percent of patients with hepatocellular carcinoma and exceed 1,000 ng per mL in 40 percent of patients with this cancer.[6] Although randomized controlled trials have not shown mortality risk benefit, the use of AFP in hepatocellular carcinoma screening continues to be debated. Retrospective studies[19,20] in Asia showed improved survival with AFP screening, but the findings of this study have not been duplicated.

Some experts use annual AFP and ultrasound screening in patients with well-compensated nonalcohol-induced cirrhosis.[20] In patients with a hepatic mass and risk factors for hepatocellular carcinoma, an AFP level above 500 ng per mL is often used in lieu of biopsy to diagnose hepatocellular carcinoma.[6]

Beta Subunit of Human Chorionic Gonadotropin

The beta subunit of human chorionic gonadotropin (β-hCG) normally is produced by the placenta. Elevated β-hCG levels most commonly are associated with pregnancy, germ cell tumors, and gestational trophoblastic disease. False-positive levels occur in hypogonadal states and with marijuana use.[7]

Both AFP and β-hCG play crucial roles in the management of patients with nonseminomatous germ cell tumors. The AFP or β-hCG level is elevated in 85 percent of patients with these tumors *(Table 1)*,[1-14] but in only 20 percent of patients with stage I disease.[8] Hence, these markers have no role in screening. Marked elevations of AFP or β-hCG are associated with very few disease states *(Table 2)*.

In patients with extragonadal disease or metastasis at the time of diagnosis, highly elevated AFP or β-hCG values can be used in place of biopsy to establish a diagnosis of nonseminomatous germ cell tumor. AFP values in excess of 10,000 ng per mL or β-hCG levels above 50,000 mIU per mL at initial diagnosis portend a poor prognosis, with a five-year survival rate of 50 percent. Similarly staged patients with lower AFP and β-hCG levels have a cure rate higher than 90 percent.[21]

Following AFP and β-hCG levels is imperative in monitoring response to treatment in patients who have nonseminomatous germ cell tumors. Patients with AFP and β-hCG levels that do not decline as expected after treatment have a significantly worse prognosis, and changes in therapy should be considered.[22] Because curative salvage therapy is possible, the tumor markers are followed every one to two months for

TABLE 2
AFP and β-hCG Levels in Germ Cell Tumors and Gestational Trophoblastic Disease

Tumor	*AFP elevation*	*β-hCG elevation*
Seminoma and dysgerminoma	Never*	Occasional, minimal
Embryonal cell carcinoma	Yes	Yes
Choriocarcinoma	No	Yes
Yolk sac tumors	Yes	No
Teratoma	No	No
Gestational trophoblastic disease†	No	Yes

AFP = alpha-fetoprotein; β-hCG = beta subunit of human chorionic gonadotropin.

**—Any detectable AFP indicates the presence of a nonseminomatous component; in this situation, the malignancy should be treated as a nonseminomatous germ cell tumor.*

†*—Gestational trophoblastic disease is not a germ cell tumor; rather, it is a rare gynecologic malignancy related to pregnancy.*

one year after treatment, then quarterly for one year, and less frequently thereafter.[8] AFP or β-hCG elevation is frequently the first evidence of germ cell tumor recurrence; a confirmed elevation should prompt reinstitution of therapy.[23]

The β-hCG level is used to diagnose gestational trophoblastic disease, a rare neoplastic complication of pregnancy. The β-hCG value is followed to assess response to treatment and to detect relapse in a manner similar to that for germ cell tumors[24] *(Table 2)*.

Cancer Antigen 125

CA 125 is a glycoprotein normally expressed in coelomic epithelium during fetal development. This epithelium lines body cavities and envelopes the ovaries.

Elevated CA 125 values most often are associated with epithelial ovarian cancer, although levels also can be increased in other malignancies.[9] CA 125 levels are elevated in about 85 percent of women with ovarian cancer, but in only 50 percent of those with stage I disease. Higher levels are associated with increasing bulk of disease and are highest in tumors with nonmucinous histology.[9] Multiple benign disorders also are associated with CA 125 elevations, presumably by stimulation of the serosal surfaces[10] *(Table 1)*.[1-14]

Insensitivity in early-stage disease and low disease prevalence limit the usefulness of CA 125 in ovarian cancer screening. In the largest study to date,[25] CA 125 levels were monitored in all patients annually for three years, and elevated values prompted ultrasound examinations. The positive predictive value was 20 percent, translating to five exploratory laparotomies for each ovarian cancer diagnosed. Survival was not improved in the women who were found through CA 125 screening to have ovarian cancer.

Randomized trials are being conducted to assess the role of CA 125 in ovarian cancer screening. Annual ultrasound examination and CA 125 screening have been advocated for women with hereditary ovarian cancer syndromes.[26]

CA 125 has been used as an adjunct in the diagnosis of pelvic masses. In postmenopausal women with asymptomatic palpable pelvic masses, CA 125 levels higher than 65 units per mL have a positive predictive value of 98 percent for ovarian cancer. Because premenopausal women have more benign causes of elevated CA 125 levels, testing for the marker is less useful in this population.[27]

Currently, ovarian cancer is treated with maximal surgical reduction, which leaves minimal clinical or radiographic disease.[26] Because studies have demonstrated concordance of CA 125 levels with disease activity, oncologists rely on CA 125 levels to guide therapeutic decisions.[28] After definitive treatment of ovarian cancer, CA 125 levels should be obtained every three months for two years, and with decreasing frequency thereafter. Elevated CA 125 levels during follow-up nearly always indicate ovarian cancer recurrence.[26]

Prostate-Specific Antigen

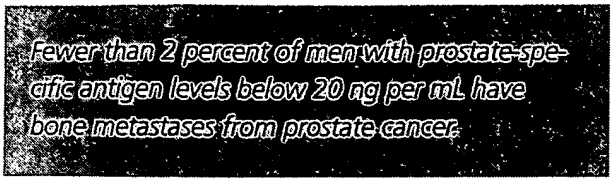
Prostate-specific antigen (PSA) is a glycoprotein produced by prostatic epithelium. The PSA level can be elevated in prostate cancer, prostatitis, benign prostatic hypertrophy, and prostatic trauma, as well as after ejaculation[12] *(Table 1)*.[1-14]

In men with prostatitis, PSA levels return to normal within eight weeks of symptom resolution. Waiting 48 hours after ejaculation to measure the PSA level has been recommended.[13] Digital rectal examination does not elevate PSA levels above normal values.[29] In men who have been taking finasteride (Proscar) for more than six months, reported PSA levels should be doubled to accurately reflect true values, because the drug is an enzyme inhibitor that suppresses normal production of PSA by the prostate gland.[30]

In prostate cancer, the positive predictive value of PSA levels greater than 4 ng per mL is 20 to 30 percent and rises to 50 percent when PSA levels exceed 10 ng per mL. Nevertheless, 20 to 30 percent of men with prostate cancer have PSA levels within normal ranges.[12]

Modifications to improve the positive predictive value of PSA testing include revised limits of normal based on age, race, velocity, density, and percentage of unbound (free) antigen. To date, these modifications have not resulted in improved outcomes. However, in patients with PSA values between 4 and 10 ng per mL, the PSA velocity and percentage of free PSA have been helpful in making clinical decisions. A velocity of 0.75 ng per mL per year is predictive of cancer.[31] When less than 10 percent of PSA is unbound, the positive predictive value for prostate cancer is 55 percent, compared with 8 percent when more than 25 percent of PSA is unbound.[32]

Prostate cancer screening remains controversial. Surrogate evidence of screening benefits include lower PSA levels[33] and earlier stage of disease at the time of initial diagnosis.[34] Limitations of screening include uncertainty about outcome benefit after treatment of localized prostate cancer,[35] potential identification of clinically insignificant tumors,[36] and attendant morbidity of treatment.[35] Experts from the American Urological Association suggest that



patients should be given sufficient information to allow them to make an informed decision about prostate cancer screening using PSA levels *(Table 3)*.[37]

If PSA testing is undertaken, an age of 40 years has been suggested for initiation of screening in black men and in all men with a family history of prostate cancer.[37] In patients without established risk factors and a minimum life expectancy of 10 years, screening could begin at age 50. If elevated PSA values are confirmed, patients should be referred for biopsy.[12] Randomized clinical trials are being conducted to assess the validity of these recommendations.

PSA levels predict the presence of metastatic disease. Patients with newly diagnosed prostate cancer and PSA levels below 20 ng per mL rarely have osseous metastasis and do not need bone scanning, because the incidence of metastatic disease in these men is lower than 2 percent.[38] In addition, computed tomographic scanning is unnecessary in men with PSA levels below 25 ng per mL.[12] At our institution, if a prostate nodule is detected, the bone scan is widely positive, and the PSA level exceeds 100 ng per mL, treatment is often instituted without performance of biopsy.

After treatment of prostate cancer, PSA levels should be obtained every six months for five years, and then annually.[39] In men who have undergone radical prostatectomy, any detectable PSA is significant.[12] Salvage radiotherapy may be appropriate in these patients if recurrence is limited to the prostate bed as determined by ProstaScint scanning, a nuclear medicine test using a radiolabeled antibody that targets only prostate tissue.

After radiotherapy, a PSA nadir is not reached for one to two years. Three consecutive elevations of the PSA level indicate biochemical relapse in previously irradiated patients.[12] Metastases do not become clinically evident for an average of eight years, and death does not occur for an average of 13 years. Thus, management decisions must include consideration of a patient's age and comorbid conditions.[40]

TABLE 3
Information for Patients About Prostate Cancer Screening

Prostate cancer is common and potentially lethal; however, more patients die with, rather than from, the disease.
Screening detects more cases of organ-confined disease, but there is no proof that this detection saves lives.
In most instances, prostate cancer is not the cause of an elevated PSA level.
Localized treatment of prostate cancer is effective but is associated with complications than can include impotence and incontinence.
It is likely that prostate cancer screening using the PSA level is beneficial in a subset of men; however, the characteristics of this subset have not been defined.

PSA = prostate-specific antigen.

Information from reference 37.

Cancer of Unknown Primary

Confusion exists about the value of tumor markers in a patient with cancer of unknown primary. Intuitively, a panel of tumor markers should help to establish the origin of the tumor. Unfortunately, most tumor markers are too nonspecific for this purpose. However, with adenocarcinoma in older men, significant PSA elevations have sufficient specificity to make the diagnosis of prostate cancer.

In poorly differentiated tumors, AFP and β-hCG levels should be ordered. Marked elevations of these tumor markers signify the presence of an extragonadal germ cell tumor. In women with peritoneal carcinomatosis or malignant ascites, treatment for ovarian cancer is instituted if the CA 125 level is elevated.[41]

Tumor markers in common use are summarized in *Table 4*.[1,5,8,12,16,24,26,27,39-41]

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The Authors

GREG L. PERKINS, M.D., currently is a family physician in Carroll, Iowa. After graduating from Rush Medical College of Rush University, Chicago, Dr. Perkins completed a family practice residency and an internal medicine/oncology fellowship at Ventura County (Calif.) Medical Center.

EVAN D. SLATER, M.D., is director of hematology/oncology at Ventura County Medical Center and assistant clinical professor at the University of California, Los Angeles (UCLA), School of Medicine. Dr. Slater received his medical degree from Duke University School of Medicine, Durham, N.C. He completed an internal medicine residency and an oncology fellowship at the University of California, San Francisco, School of Medicine.

GEORGANNE K. SANDERS, M.D., is a hospitalist at Ventura County Medical Center and assistant clinical professor at UCLA School of Medicine. Dr. Sanders graduated from Pennsylvania State University College of Medicine, Hershey, and completed a family practice residency at Ventura County Medical Center.

JOHN G. PRICHARD, M.D., is director of internal medicine at Ventura County Medical Center and associate clinical professor at UCLA School of Medicine. After graduating from the University of California, Irvine, College of Medicine, Dr. Prichard completed a family practice residency and an internal medicine fellowship at Ventura County Medical Center.

Address correspondence to Greg L. Perkins, M.D., 405 S. Clark., Carroll, IA 51401 (e-mail: gperkins@mcfarlandclinic.com). Reprints are not available from the authors.

TABLE 4
Tumor Markers In Common Use

Tumor marker	Primary tumor(s)	Use of tumor marker: Screening	Use of tumor marker: Diagnosis	Follow-up after primary treatment	Monitoring of treatment response
CA 27.29[1]	Breast cancer	No	No	Consider in patients at high risk for recurrence; obtain CA 27.29 level every 4 to 6 months.	Helpful
CEA[16]	Colorectal cancer	No	No	In patients at high risk for recurrence, obtain CEA level every 2 to 3 months for at least 2 years.	Very helpful
CA 19-9[5]	Pancreatic cancer, biliary tract cancer	No	Selected pancreatic masses	No	Helpful
AFP[8,20,41]	Hepatocellular carcinoma, nonseminomatous germ cell tumor	No*	Poorly differentiated cancer of unknown primary; patients with cirrhosis and a liver mass	In patients treated for nonseminomatous germ cell tumor, obtain AFP and β-hCG levels every 1 to 2 months for 1 year, then quarterly for 1 year, and less frequently thereafter.	Essential in patients treated for nonseminomatous germ cell tumor; very helpful in patients treated for hepatocellular carcinoma
β-hCG[8,24,41]	Nonseminomatous germ cell tumor, gestational trophoblastic disease	No	Poorly differentiated cancer of unknown primary; gestational trophoblastic disease	Nonseminomatous germ cell tumor: see AFP above. In patients treated for gestational trophoblastic disease, obtain β-hCG level once a month for 6 to 12 months.	Essential in patients treated for nonseminomatous germ cell tumor or gestational trophoblastic disease
CA 125[26,27,41]	Ovarian cancer	No†	Adjunct for diagnosis of pelvic mass in postmenopausal women; malignant ascites in women with cancer of unknown primary	Obtain CA 125 level every 3 months for 2 years, then less frequently.	Very helpful
PSA[12,39-41]	Prostate cancer	Yes	Adenocarcinoma of unknown primary; widely positive bone scan and prostate mass	Obtain PSA level every 6 months for 5 years, then annually.[39] Any detectable PSA after radical prostatectomy indicates recurrence. Three consecutive PSA elevations after radiation therapy indicate recurrence.	Very helpful

CA = cancer antigen; CEA = carcinoembryonic antigen; AFP = alpha-fetoprotein; β-hCG = beta subunit of human chorionic gonadotropin; PSA = prostate-specific antigen.

**—Except in highly selected patients with nonalcoholic-induced cirrhosis.*

†—Except in heritable ovarian cancer syndromes.

Information from references 1, 5, 8, 12, 16, 24, 26, 27, and 39 through 41.

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